REMARKS

Claim Amendements

Claims 1, 31 and 148-149 are currently pending herein. No new matter has been added.

Rejoinder

Applicants believe that Claims 1 and 31 are in condition for allowance and, therefore, respectfully request that withdrawn Claims 3, 5, 10-16, 18, 32, 40, 42, 95, 99 and 147-149 be rejoined.

Rejection of Claims 1 and 31 Under requirements of 35 U.S.C. §103(a)

Claims 1 and 31 are rejected under 35 U.S.C. §103(a) as being unpatentable over Yu et al, in view of Kandimalla et al. and Liu et al.

Applicants respectfully disagree that the cited art teaches or suggests an oligonucleotide comprising the instantly claimed RpG dinucleotide, or the linking of two such oligonucleotides via a non-nucleotidic linker. Furthermore, Applicants disagree with the Office Action's characterization of the cited art and the alleged motivation to combine the cited art to reach the instantly claimed compound.

The Office Action states that Yu et al. teaches an immunomer compound comprising at least two phosphorothioate (PS) oligonucleotides linked at their 3'-ends, wherein at least one of the oligonucleotides is an oligonucleotide having an accessible 5'-end and comprises an immunostimulatory C(ps)G dinucleotide motif.

The Office Action states that although Yu does not teach that the immunomer comprises a psC*psG dinucleotide motif, Kandimalla taught the synthesis of phosphorothioate CpG immunostimulatory oligonucleotides comprising a psC*psG dinucleotide motif, wherein the C* moiety represents a monocyclic or bicyclic cytosine analogue.

Finally, the Office Action states that although neither Yu nor Kandimalla teach the cytosine is substituted for 2-oxo-7-deaza-8-methyl-purine, at the time of invention Liu taught the substitution of a cytosine for pyrrolo-dc in nucleic acids and oligonucleotides.

In relying on these interpretations of the cited art, the Office Action goes on to commit several reversible errors as follows. The Office Action (1) incorrectly states that Yu teaches or suggests an immunomer according to the instantly claimed invention, (2) incorrectly states that

Yu, in combination with Kandimalla, teach or suggest an immunomer having a C*pG dinucleotide, (3) incorrectly states that Kandimalla provides a motivation, with a reasonable expectation of success, to modify the C of the CpG dinucleotide to arrive at the instantly claimed invention, and (4) incorrectly interprets the teachings of Liu to be relevant to the instantly claimed invention. Any one of these errors is fatal to the present rejection. Each source of reversible error is further addressed below.

(1) Yu does not teach an "immunomer"

Yu teaches two (2) oligonucleotides linked directly at their 3'-ends. Yu is completely silent regarding the structure of an "immunomer", i.e., a compound comprising at least at least two oligonucleotides linked at their 3' ends, internucleoside linkages, functionalized nucleobase or sugar to a non-nucleotidic linker, wherein at least one of the oligonucleotides is an oligonucleotide having an accessible 5' end and comprising an immunostimulatory dinucleotide.

(2) **Yu, in combination with Kandimalla, fails to teach or suggest an immunomer having a C*pG dinucleotide**

As stated above, Yu does not teach or suggest the instantly claimed immunomer structure and Kandimalla fails to provide the teachings that Yu lacks. Specifically, Kandimalla only describes the use of linear CpG-containing oligonucleotides and fails to teach or suggest at least two oligonucleotides linked at their 3' ends, internucleoside linkages, functionalized nucleobase or sugar to a non-nucleotidic linker, wherein at least one of the oligonucleotides is an oligonucleotide having an accessible 5' end and comprising an immunostimulatory dinucleotide.

(3) Kandimalla does not provide the motivation to substitute cytosine with pyrrolo-dc

As stated by Applicants in response to previous Office Actions, which is incorporated herein by reference, Kandimalla (2001) teaches that a YpG-containing oligonucleotide in which Y was deoxy-P-base nucleoside (referred to as "the first bicyclic non-natural cytosine" by the Office Action) showed **little or no immunostimulatory activity** (see page 809, column 2, lines 22-24)(emphasis added). The Office Action fails to explain how one skilled in the art would be motivated, with a reasonable expectation of success, to make this "simple" substitution with a

"second bicyclic non-natural cytosine" considering the first bicyclic non-natural cytosine was not functional.

Rather, the Office Action's comments regarding obviousness merely amount to an assertion that one of ordinary skill in the art would have been able to arrive at the Applicants' invention because he had the necessary skills to carry out the requisite steps. There must, however, still be prior art that suggests the claimed invention in order for a *prima facie* case of obviousness to be made out. In other words, there must be "some articulated reasoning with some rationale underpinning to support the legal conclusion of obviousness" (*KSR International Co. v. Teleflex Inc.,* 550 U.S. 398, 418 (2007)). The Office Action has failed to provide a sufficient factual basis to support the conclusion that the applied prior art teaches or suggests all of the claim limitations and that the claimed invention is, therefore, obvious.

At most, Kandimalla only adds an invitation "to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it" *In re O'Farrell*, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988). Such a rational was found to be insufficient to support a *prima facie* case of obviousness in *In re O'Farrell* and it is insufficient here.

(4) Liu is improperly applied non-analogous art

According to the Office Action, Liu teaches that pyrrolo-dc is advantageous because it is intrinsically highly fluorescent, with excitation and emission maxima far from those of DNA and protein, making it ideal for probing protein-nucleic acid interactions. Applicants, however, would like clarification as to the relevance of this teaching to the instantly claimed invention.

The field of the present invention is oligonucleotide-based compounds that are immunostimulatory in mammalian systems. At the time Applicants' invention was made, it was known that a CpG dinucleotide moiety was essential to the immune stimulatory activity of such oligonucleotide-based compounds. Claim 18 recites a solution to the problem of providing new immunomer compounds comprising an immunostimulatory dinucleotide having the structure C*pG (wherein C*=R) while retaining (and modifying) immunostimulatory activity. Despite the fact that Liu is completely silent regarding immunostimulatory oligonucleotides, CpG motifs, or whether such a motif can be modified, particularly with pyrrolo-dc, and still retain its

immunostimulatory activity, the Office Action states that one of skilled in the art would look to Liu in the context of CpG-containing oligonucleotides.

In an attempt to support the rejection, and the relevance of Liu to the instantly claimed invention, the Office Action cites *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945) ("The selection of a known material based on its suitability for its **intended use** supported a prima facie obviousness determination" (emphasis added)) and In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982) ("When substituting equivalents known in the prior art for the **same purpose**, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious" (emphasis added)).

The Federal Circuit discussed the requirements for a prior art reference to be properly considered as analogous art in *In re Oetiker*, 977 F.2d 1443 (1992), stating:

> In order to rely on a reference as a basis for rejection of the applicant's invention, the reference must either be in the field of the applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned. *See In re Deminski,* 796 F.2d 436, 442, 230 USPQ 313, 315 (Fed.Cir.1986). Patent examination is necessarily conducted by hindsight, with complete knowledge of the applicant's invention, and the courts have recognized the subjective aspects of determining whether an inventor would reasonably be motivated to go to the field in which the examiner found the reference, in order to solve the problem confronting the inventor. We have reminded ourselves and the PTO that it is necessary to consider "the reality of the circumstances", *In re Wood,* 599 F.2d 1032, 1036, 202 USPQ 171, 174 (CCPA 1979)-in other words, common sense-in deciding in which fields a person of ordinary skill would reasonably be expected to look for a solution to the problem facing the inventor.

In the present case, Liu is clearly not in Applicants' field of endeavor, nor is it reasonably pertinent to the problem Applicants sought to solve. The intended use and/or purpose of Liu is to gain "an understanding of the nature of the melted bubble which moves with the RNA polymerase active site" during transcription elongation.

This is clearly not the intended use of the instantly claimed invention. Nowhere in the instant specification is it even postulated that the instantly claimed immunomer can be used to study the melted bubble. Nor is there any teaching or suggestion in Liu that pyrrolo-dc can be substituted in the CpG dinucleotide of a CpG-containing oligonucleotide while still maintaining the immunostimulatory properties of the oligonucleotide. Applying "common sense", it should be manifestly clear that one skilled in using oligonucleotides to induce an immune response in mammalian cells would not look to Liu's system for studying the melted bubble.

Additionally, it appears that the Office Action is indicating that Liu's method of studying DNA-protein interaction would be useful in elucidating how a CpG-containing oligonucleotide interacts with the TLR-9 receptor. However, as stated above, Kandimalla demonstrated that a first bicyclic non-natural cytosine substitution for C of the CpG was inactive (i.e., that the oligonucleotide of Kandimalla did not functionally interact with the protein receptor). Therefore, one skilled in the art would not be motivated to look to Liu's method, with a reasonable expectation of success, to use a second bicyclic non-natural cytosine to bind the TLR-9 receptor and be useful.

As the use of pyrrolo-dc in Liu and instant Claim 18 are not for the same purpose, the case law relied upon by the Office Action further supports the lack of *prima facie* obviousness. As such, the cited reference, alone and in combination, fail to teach or suggest the instantly claimed invention. Reconsideration and withdrawal of the rejection is respectfully requested.

Provisional obviousness-type double patenting

Claims 1 and 31 are provisionally rejected over various claims of copending Application Nos. 10/361,111; 10/865,245; 10/925,873; 11/153,054; and 11/174,002.

As stated by the Examiner, this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Please note that, with regards to patent term, U.S. Application Nos. 10/361,111; 10/865,245; 10/925,873; 11/153,054; and 11/174,002 are the later filed applications.

Therefore, if this provisional double patenting rejection is the only remaining rejection in the application, Applicants request that the Examiner withdraw the rejection in the instant [earlier filed] application thereby permitting this application to issue without need of a terminal disclaimer. (See MPEP §804(I)(B)). Once the instant claims have been allowed and these rejections have been withdrawn, Applicants will then consider filing a Terminal Disclaimer or take any other action deemed necessary in the later filed, copending applications.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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